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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,574	11/07/2001	Fabienne MacKay	08201.0024-01000	9312

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FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
1300 I. Street, N.W.
Washington, DC 20005-3315

EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,574	MACKAY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/31/03, is acknowledged.

2. Claims 63- 84 are pending and under consideration in the instant application.

3. The specification on page 1 should be amended to reflect the status of parent application No. 09/911,777.

4. In view of the amendment filed on 12/31/04, only the following rejections are remained.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 63-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a method for treating a mammal having Sjogren's syndrome, the method comprising administering to the mammal a composition "comprising" soluble BAFF-R in an amount and for a period of time sufficient to reduce immunoglobulin production in the mammal in claim 63, wherein the mammal is a human, in claim 64, a mouse in claim 65, wherein the mouse is a BAFF Tg mouse in claim 66, wherein the salivary gland of the mammal is infiltrated by MZ-like B cells in claim 67, wherein BAFF-R is human/murine in claim 68/70, wherein the soluble BAFF-R "comprises" any "portion of" SEQ ID NO: 27/28 in claim 69/71, wherein the soluble BAFR comprises an immunoglobulin Fc domain in claim 72, wherein the immunoglobulin Fc domain is a human immunoglobulin Fc domain in claim 73 or a method of treating a mammal having Sjogren's syndrome, the method comprising administering to the mammal a composition comprising soluble BAFF-R in an amount and for a period of time sufficient to reduce B cell growth in the mammal in claim 74, wherein the mammal is a human in claim 75, a mouse in claim 76, wherein the mouse is a BAFF Tg mouse in claim 77, wherein the salivary gland of the mammal is infiltrated by MZ-like B cells in claim 78, wherein BAFF-R is human/murine in claim 79/81, wherein the soluble BAFF-R "comprises" any "portion" of SEQ ID NO: 27/28 in claim 80/82, wherein the soluble BAFF-R comprises an immunoglobulin Fc domain in claim 83, wherein the immunoglobulin Fc domain is a human immunoglobulin Fc domain in claim 84. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 7/30/03.

Further, the term "comprises", in claims 69, 71, 80 and 82, is an open-ended and expand the amino acid portion of SEQ ID NOs: 27/28 to include additional non disclosed amino acids on either or both sides of the N-terminal or C-terminal of the portions. Further, the specification fails to provide sufficient guidance as to which core structure of SEQ ID NO: 27/28 is essential for maintain its functional activity to reduce B cell growth and which changes can be made in the structure of SEQ ID NO: 27/28 and still maintained the same function.

The specification in fact does not provide any soluble BAFF-R fragment or portion thereof. The specification does not disclose what region of the BAFF-R constitutes a soluble BAFF-R. Further, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various amino acids portions recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for BAFF ligand activity. Without detailed direction as to which amino acid sequences are essential to the function of the polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant claims would share the ability to bind BAFF ligand.

The Declaration of Leslie A. McDonell, filed 12/31/03, stating that the sequences set forth under SEQ ID NO: 27 and SEQ ID NO: 28 and the accession numbers are the same as disclosed in Figure 1 in Thompson et al. (2001), Science, 293:2108, previously incorporated by reference at page 17, line 5-6, of the specification, is acknowledged. However, it is noted that SEQ ID NO: 27 is different than the human BAFF-R taught by Thompson et al Science 293:2108-211 (2001). Thompson et al teach a 184 amino acid BAFF-R, while claimed SEQ ID NO: 27 is a 185 amino acid sequence. Further, it is noted that SEQ ID NO: 27 inserts an amino acid position 46, which is Xaa.

Applicant's arguments, filed 12/31/03, have been fully considered, but have not been found convincing.

Applicant argues that Dang is not relevant to the present invention. Dang shows that administration of TGF-β to TGF-β-null mice fails to reduce autoantibody production. The claims, however, require administration of BAFF-R, and not TGF-β. TGF-β and BAFF-R are dissimilar molecules, both structurally and functionally. To illustrate this point, Applicants attach results of a comparison between human TGF-β1 (Accession No. P01 137) and BAFF-R (Accession No. AF373846) sequences. Applicant submits that the sequence comparison, show no significant similarity exists between TGF-β1 and BAFF-R. Applicant argues that there is no apparent functional similarity between the two molecules. Applicant asserts that TGF-β is a ligand of the TGF-β superfamily, whereas BAFF-R belongs to the TNF receptor family. Further, Applicant argues that unlike BAFF-R, TGF-β does not bind to BAFF; TGF-β is not even a receptor. Applicant submits that Dang does not mention BAFF, BAFF-R, or any other TNF family receptor or ligand. Applicant argues that even if Dang did

show that TGF-β had a particular effect. This would not allow a skilled artisan to conclude that BAFF-R would (or would not) have the same or a similar effect.

While the TGF-β and BAFF-R of TNF family are structurally different molecules, both TGF-β and TNF-α are associated with anti-SS B antibody production. Further, similar to Dang's TGF-β1 null mutation mice, the instant specification's aged BAFF Tg mice develop "Sjogren's syndrome" (see specification page 6, lines 22-26). Therefore, it is unpredictable if treating the aged BAFF Tg mice with BAFF-R would suppress autoantibody production and treat SS patients.

Applicant contends that the instant specification teaches that as a result of BAFF overexpression, BAFF transgenic mice develop Sjögren-like syndrome as they age. Applicant directs the Examiner's attention to Examples 7-11. Applicant submits that the BAFF Tg mice develop proteinuria, Lupus-like disease, severe sialadenitis, and decreased saliva production. Applicant asserts that the working examples support the concept that an imbalance in BAFF production is a major factor contributing to the development of SS. This concept is further supported by the finding that many patients with primary SS have high levels of BAFF in the serum. In particular, the specification discloses high incidence (36%) of abnormally high levels of BAFF in the serum of patients with SS. See Example 12.

However, the specification fails to disclose the efficacy of the soluble BAFF-R on Sjögren's syndrome. Further, SS disease is not the only disease that correlates with high levels of BAFF ligand, rheumatoid arthritis, myasthenia gravis and SLE also show high level of BAFF concentration which correlate with disease related autoantibodies.

Applicant draws the Examiner's attention to Mariette *et al.* Ann Rheum Dis. 2003 Feb;62(2):168-171 to support his position that there is a correlation between human SS and high levels of BAFF .

However, Marriette *et al* provide correlation between SS and BAFF ligand concentration without providing efficacy of the BAFF-R on Sjögren's syndrome.

7. The declaration of Susan Kalled, filed 12/31/03, under 37 CFR1.132 is insufficient to overcome the rejection of 35 U.S.C. 112, first paragraph under enablement because the six-month-old BAFF Tg mice is not recognize as an acceptable animal model for human SS. Further, the BAFF-Tg animal is constitutively expressing BAFF (under the control of liver specific regulatory sequences) and treating with BCMA-Fc just tittering down the ligand and hence neutralizing the effects of the BAFF ligand on the on B-cells. In addition, the elevated serum proteinuria is associated with other diseases such as lupus and is not limited to SS disease. The declaration did not address whether the BAFF Tg mice is acceptable animal models to study early events, immune manipulation, and drug therapy as well as identify and control immune reactions. The Declaration further did not fulfill certain criteria and clinical features found in human SS disease, such as dry mouth and eyes, serologic abnormalities (hypergammaglobulinemia, ANA, anti-Ro and anti-La antibodies, and rheumatoid factor, and

histopathologic changes). Further, the increased BAFF concentrations in body fluids is not particular to SS, but have been found in patients with RA, systemic lupus erythematosus (SLE) which correlate with disease related autoantibodies. Finally, the declaration show that BAFF Tg mice treated with BCMA-Fc inhibited the production of immunoglobulin. However, the claimed invention is administering soluble BAFF-R-Fc and thus does not address the point at hand. The declaration fails to address the effect of treating the BAFF Tg mice with "BCMA-Fc" on sialadenitis and saliva production found in SS disease.

8. Claims 63-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 7/30/03.

Applicant is not in possession of a method for treating a mammal having Sjogren's syndrome, the method comprising administering to the mammal a composition "comprising" soluble BAFF-R in an amount and for a period of time sufficient to reduce immunoglobulin production in the mammal in claim 63, wherein the mammal is a human, in claim 64, a mouse in claim 65, wherein the mouse is a BAFF Tg mouse in claim 66, wherein the salivary gland of the mammal is infiltrated by MZ-like B cells in claim 67, wherein BAFF-R is human/murine in claim 68/70, wherein the soluble BAFF-R "comprises" any "portion of" SEQ ID NO: 27/28 in claim 69/71, wherein the soluble BAFR comprises an immunoglobulin Fc domain in claim 72, wherein the immunoglobulin Fc domain is a human immunoglobulin Fc domain in claim 73 or a method of treating a mammal having Sjogren's syndrome, the method comprising administering to the mammal a composition comprising soluble BAFF-R in an amount and for a period of time sufficient to reduce B cell growth in the mammal in claim 74, wherein the mammal is a human in claim 75, a mouse in claim 76, wherein the mouse is a BAFF Tg mouse in claim 77, wherein the salivary gland of the mammal is infiltrated by MZ-like B cells in claim 78, wherein BAFF-R is human/murine in claim 79/81, wherein the soluble BAFF-R "comprises" any "portion" of SEQ ID NO: 27/28 in claim 80/82, wherein the soluble BAFF-R comprises an immunoglobulin Fc domain in claim 83, wherein the immunoglobulin Fc domain is a human immunoglobulin Fc domain in claim 84.

Applicant's arguments, filed 12/31/03, have been fully considered, but have not been found convincing.

Applicant argues that an adequate written description can be achieved by (1) an alignment of human and mouse sequences reveals unifying structural features of the claimed genus, (2) human and murine BAFF-R exhibit a 55% identity in the extracellular domain of about 80 amino acids, (3) Fersht teaches that tertiary structure of these two proteins is expected to be identical and Thompson confirms that human and murine BAFF-R do, in fact have the same functionality, (4) human and mouse are phylogenetically divergent, with most other BAFF-R species being expected to have a similar or higher percent identity than that between human and murine sequences, and (5) according to Fersht, a substantial number of BAFF-R species are expected to

retain the tertiary structure/activity required by the claimed methods. Therefore, human and murine sequences are representative of the claimed genus of soluble BAFF-R.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

However, in the instant case, there is no described or art-recognized correlation or relationship between the structure of the invention, the BAFF-R and it's inhibition of antibody production function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of BAFF-R or soluble BAFF-R comprises a portion of SEQ ID NO:27/28, wherein the portion binds to BAFF which retain the features essential to the instant invention.

In order to satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563. The written-description requirement can be satisfied "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

9. The following new ground of rejection is necessitated by the amendment filed 12/31/03.

10. The amendment filed 12-31-03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment filed on 12-31-03 to the sequence listing and the paragraph on page 17, lines 4-7 to add SEQ ID NO: 27 represents a departure from the specification and the claims as originally filed. Applicant points out to the "essential material" from Thompson et al (2001) Science,

293:2108, incorporated by reference for support. However, the Thompson et al have no support for the new added of SEQ ID NO: 27. It is noted that Thompson et al teach a 184 amino acid sequence while the added SEQ ID NO: 27 comprises 185 amino acid sequence. It is noted that SEQ ID NO: 27 contain an extra amino acid Xaa at position 46.

Applicant is required to cancel the new matter in the response to this Office action.

11. Claims 63-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "SEQ ID NO: 27" claimed in claims 69, and 80, the phrase "for a period of time sufficient to reduce immunoglobuline production in the mammal" claimed in claim 63, lines 3-4, the phrase " a portion of SEQ ID NO: 27 that binds to BAFF" claimed in claims 69 and 80, line 1-2, the phrase " a portion of SEQ ID NO: 28 that binds to BAFF" claimed in claims 71 and 82, lines 1-2, the phrase "for a period of time sufficient to reduce B cell growth in the mammal" claimed in claim 74, lines 3-4, represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 12/31/03 points to the specification at page 6, line 24-26, page 17, line 3, page 8, lines 6-7, page 16, lines 27-29, page 17, lines 6-7, and original claims 10, 11 , 52, 53, and 57 and the Declaration of Leslie A. McDonell, filed 12/31/03 for support for the newly added limitations "SEQ ID NO: 27", "for a period of time sufficient to reduce immunoglobuline production in the mammal", " a portion of SEQ ID NO: 27 that binds to BAFF", " a portion of SEQ ID NO: 28 that binds to BAFF", "for a period of time sufficient to reduce B cell growth in the mammal". However, the specification does not provide a clear support for such limitations. It is noted that SEQ ID NO: 27 is different than the human BAFF-R taught by Thompson et al Science 293:2108-211 (2001). Thompson et al teach a 184 amino acid BAFF-R, while claimed SEQ ID NO: 27 is a 185 amino acid sequence. Further, it is noted that SEQ ID NO: 27 inserts an amino acid position 46, which is Xaa. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
March 19, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600